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Metal-Free Direct Arylations of Indoles and Pyrroles with Diaryliodonium Salts

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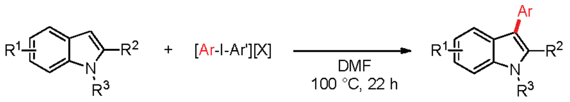
ABSTRACT



Direct arylations of indoles and pyrroles with differently substituted diaryliodonium salts were shown to efficiently proceed in the absence of metal catalysts.

Direct arylations of otherwise unreactive C–H bonds have emerged in recent years as attractive alternatives to traditional cross-coupling reactions with organometallic reagents.[1] Particularly, the direct functionalization of indole derivatives has received significant attention,[2] because this scaffold is omnipresent in biologically active compounds and natural products.[3] Remarkable progress in metal-catalyzed direct arylations of electron-rich (hetero)arenes was recently accomplished through the use of diaryliodonium salts as arylating reagents.[2b,4] During studies directed toward the development of ruthenium-catalyzed[5] C–H bond functionalizations on heteroarenes we observed that C–H bond arylations of indoles and

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(1) Select recent reviews on metal-catalyzed C–H bond functionalizations: (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931. (b) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725–748. (c) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503–4513. (d) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57–84. (e) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677–685. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (g) Fagnou, K. *Top. Curr. Chem.* **2010**, *292*, 35–56. (h) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654–2672. (i) Lei, A.; Liu, W.; Liu, C.; Chen, M. *Dalton Trans.* **2010**, *39*, 10352–10361. (j) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866–4877. (k) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (l) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096–2098. (m) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242–3272. (n) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087–4109. (o) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269–10310. (p) Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (q) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (r) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883. (s) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (t) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013–3039. (u) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (v) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238 and references cited therein.

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(5) Reviews: (a) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211–229. (b) Ackermann, L. *Pure Appl. Chem.* **2010**, *82*, 1403–1413.

(6) For recent progress in direct arylations under transition-metal-free reaction conditions, see: (a) Shirakawa, E.; Itoh, K.-I.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537–15539. (b) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nat. Chem.* **2010**, *2*, 1044–1049. (c) Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 16737–16740 and references cited therein. For a pioneering example, see: (d) Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673–4676. For reviews, see:(e) Yanagisawa, S.; Itami, K. *ChemCatChem* **2011**, *3*, DOI: 10.1002/cctc.201000431. (f) Leadbeater, N. E. *Nat. Chem.* **2010**, *2*, 1007–1009.

(7) For representative recent examples of metal-free arylations with diaryliodonium salts, see: (a) Jalalian, N.; Ishikawa, E. E.; Silva, L. F.; Olofsson, B. *Org. Lett.* **2011**, *13*, 1552–1555. (b) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 3334–3337. (c) Morimoto, K.; Yamaoka, N.; Ogawa, C.; Nakae, T.; Fujioka, H.; Dohi, T.; Kita, Y. *Org. Lett.* **2010**, *12*, 3804–3807. (d) Eastman, K.; Baran, P. S. *Tetrahedron* **2009**, *65*, 3149–3154. (e) Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009**, *131*, 1668–1669. (f) Dohi, T.; Ito, M.; Morimoto, K.; Iwata, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 1301–1304 and references cited therein. (g) See also ref 7 in the Supporting Information.

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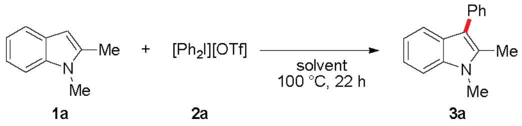
pyrroles occur in the absence of transition metal catalysts,[6,7] on which we wish to report herein.

At the outset of our studies, we tested various reaction conditions for the direct functionalization of indole **1a** with diaryliodonium salt **2a** (Table 1).[8] Interestingly, we observed that direct arylations under metal-free reaction conditions proved viable in toluene, NMP, *t*-AmOH, or DMF as the solvent, the latter of which was employed for further optimization studies.

Table 1. Effect of Solvents on Direct Arylation of Indole **1a**[a]

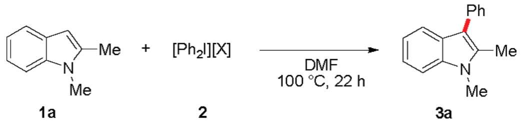


entry	solvent	yield
1	$Br_2CHCHBr_2$	--
2	$Cl_2CHCHCl_2$	3%[b]
3	1,4-dioxane	11%
4	PEG-400	--
5	PhMe	25%
6	AcOH	7%[b]
7	*t*-AmOH	39%
8	DMA	8%[b]
9	NMP	20%
10	DMF	38%
11	DMF	43%[c]

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.55 mmol), solvent (2.0 mL), 100 °C, 22 h; isolated yields. [b] GC-conversion with *n*-tridecane as standard. [c] **1a** (1.00 mmol).

Subsequently, we probed the effect exerted by the counteranions of salts **2**, which showed that satisfactory results could be obtained with diaryliodonium tetrafluoroborates, hexafluorophosphates, trifluoroacetates, or tosylates (Table 2, entries 1–6), while the corresponding bromides failed to deliver the desired product **3a** (entry 7).

Table 2. Effect of the Counteranions[a]

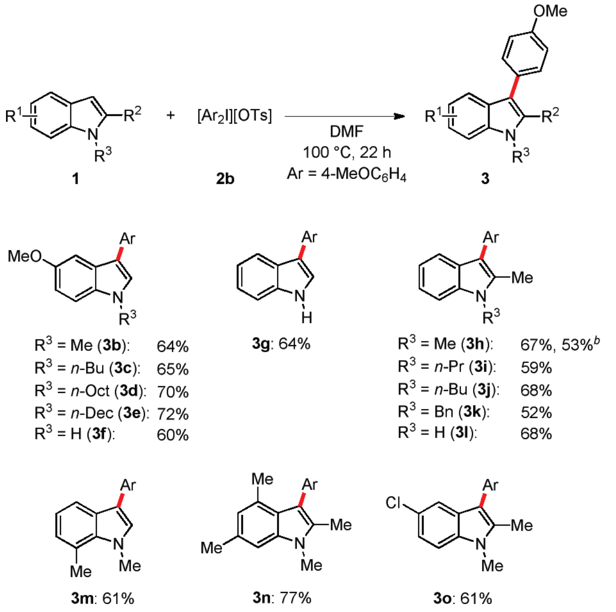


entry	X	yield
1	OTf	38%
2	BF_4	40%
3	PF_6	58%
4	OTFAc	54%
5	OTs	47%
6	OTs	54%[b]
7	Br	---

[a] Reaction conditions: **1a** (0.50 mmol), **2** (0.55 mmol), DMF (2.0 mL), 100 °C, 22 h. [b] **2** (1.00 mmol).

With optimized reaction conditions in hand, we probed the scope of metal-free direct arylations with differently substituted indoles employing dianisyliodonium tosylate (**2b**) (Scheme 1). Notably, *N*-alkyl indoles **1** were converted efficiently, as were free (*NH*)-indoles. More hindered 2-substituted indoles **1** reacted with comparable efficacy, thereby yielding products **3h**–**3l**. Decoration on the aromatic moiety of indoles **1** was well tolerated, which among others set the stage for the synthesis of chloro-substituted product **3o**.

Scheme 1. Scope of Metal-Free Direct Arylations of Indoles **1**[a]



[a] Reaction conditions: **1** (0.50 mmol), **2b** (1.00 mmol), DMF (2.0 mL), 100 °C, 22 h. [b] **2b** (0.55 mmol); isolated yields.

Direct arylations of indoles **1** occurred with excellent site-selectivities to predominantly yield the C-3 arylated products. However, it is noteworthy that small amounts of the C-2 functionalized indoles **3pb** and **3qb** were isolated when using starting materials **1p** and **1q**, respectively (Scheme 2). Here, best results were obtained with DMF or toluene as the solvent.[9]

The C–H bond functionalization protocol was not limited to the direct introduction of a 4-anisyl substituent but allowed for the preparation of products **3r**–**3u** as well (Scheme 3).[10,11]

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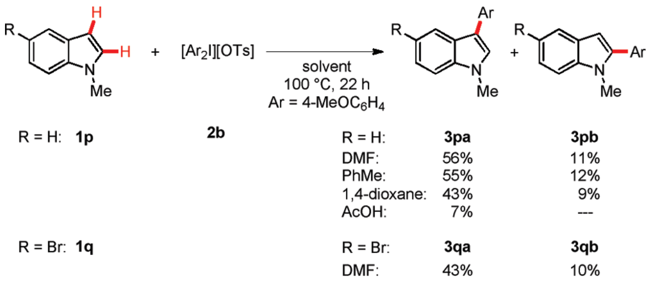
(8) All direct arylation reactions reported herein were performed in new glassware using new stirring bars. Representative starting materials **1** and **2** were analyzed by ICP-MS, which revealed only trace amounts of transition metals (*inter alia* < 1 ppm Pd, Rh, and Ru; < 10 ppm Cu).

(9) For a representative study on the effect of solvents on palladium-catalyzed oxidative arylations of indoles with arenes, see: Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. *Tetrahedron Lett.* **2008**, *49*, 4050–4053.

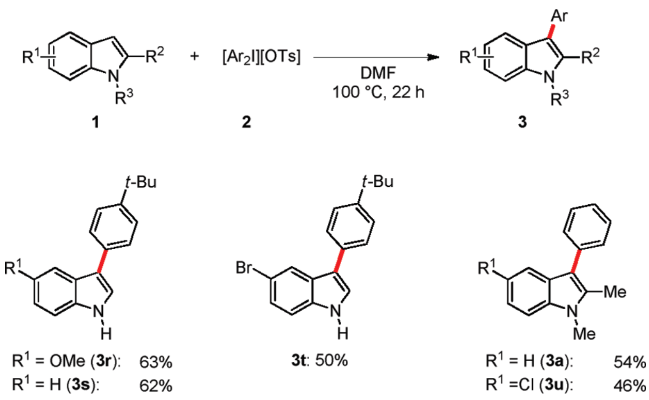
(10) Under otherwise identical reaction conditions, the addition of 2 equiv of 2,6-di-*tert*-butylpyridine afforded product **3s** in a comparable yield of 69%.

(11) Small amounts of the corresponding C-2 arylated products (2–8%) were formed during the preparation of products **3r**–**3t**, as indicated by GC/MS analysis.

Scheme 2. Direct Arylations of 2,3-Unsubstituted Indoles **1p** and **1q**

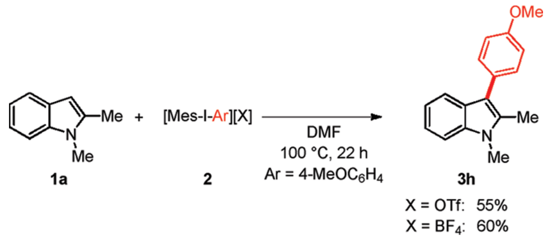


Scheme 3. Scope of Direct Arylations with [Ar$_2$I][OTs] **2**



Likewise, unsymmetrically substituted diaryliodonium salts **2** were found to be suitable arylating reagents, which resulted in the preferential transfer of the less sterically hindered aromatic moiety (Scheme 4).

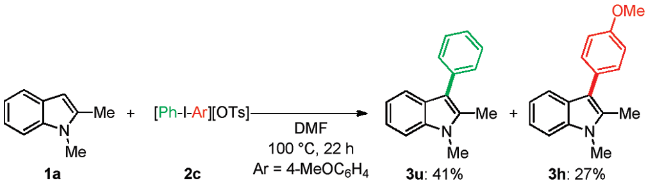
Scheme 4. Direct Arylations with Unsymmetrically Substituted Salts **2**



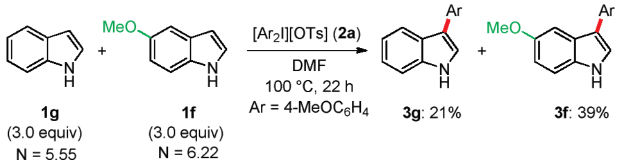
An additional intramolecular competition experiment with iodonium salt **2c** bearing two different aryl substituents with comparable steric demand highlighted that the less electron-rich group is introduced predominantly (Scheme 5).

Moreover, intermolecular competition experiments with an excess of differently substituted indoles clearly revealed a strong correlation with Mayr's nucleophilicity parameter *N*[12] (Scheme 6).

Scheme 5. Intramolecular Competition Experiment with Salt **2c**

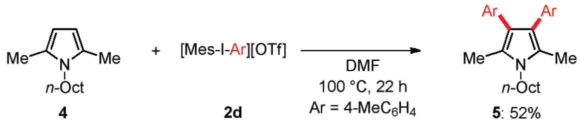


Scheme 6. Intermolecular Competition Experiment



On the basis of these experiments, we finally probed pyrrole **4** as a substrate (1,2,5-trimethylpyrrole: *N* = 8.69),[13] which delivered the desired product **5** (Scheme 7).

Scheme 7. Direct Arylation of Pyrrole **4**



In summary, we have reported on efficient direct arylations of indoles with diaryliodonium salts in the absence of metal catalysts. Importantly, the protocol proved broadly applicable, thereby enabling C–H bond functionalizations of free (*NH*)- as well as *N*-substituted indoles and pyrroles.

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Supporting Information Available. Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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